REMARKS

Formal Matters

Claims 22-51 are pending in this application. Claims 1-21 were previously canceled without prejudice to later prosecution. New claims 22-51 were previously added without the addition of new matter. No claim is amended in this response.

Rejection Under 35 U.S.C. § 103(a) (Rajkumar, T. et al. in view of Orlandi et al., Cabilly et al., Boss et al., Robinson et al., Ward et al., Queen et al, and Huston et al.)

Claim 22-33 and 36-51 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rajkumar T. et al. (Br. J. Cancer (1994) 70:459-467, IDS 39) in view of Orlandi et al. (PNAS USA (1989) 86:3833-3837), Cabilly et al. (US 4,816,567, issued 3/89), Boss et al. (US 4,816,397, issued 3/89), Robinson et al. (US 5,618,920, filed 4/94), Ward et al. (Nature (1989) 341:544-546), Queen et al. (PNAS (1989) 86:10029-10033), and Huston et al. (US5,258,498, issued 11/93). Applicants respectfully traverse the rejection as applied and as it might be applied to the currently pending claims for the reasons provided below.

Applicants' claimed invention. Applicants claim isolated nucleic acids encoding antibodies, which antibodies (1) bind to ErbB3 protein and reduce heregulin-induced formation of an ErbB2-ErbB3 protein complex in a cell expressing ErB2 and ErbB3 (independent claim 22); or bind ErbB3 and increases binding of heregulin for ErbB3 protein (independent claim 30), or bind ErbB3 and reduce heregulin binding thereto (independent claim 32), or wherein the antibody reduces ErbB2-ErbB3 complex formation, it also reduces heregulin-induced ErbB2 activation in a cell which expresses ErbB2 and ErbB3. Applicants further claim a vector or host cell comprising the claimed nucleic acids and methods of making an antibody encoded by a claimed nucleic acid by expressing and recovering the antibody and/or conjugating the recovered antibody with a cytotoxic agent or enzyme.

Rajkumar et al. as a whole. Rajkumar et al. (Br. J. Cancer (1994) 70:459-467) disclose an antibody (SGP1) that binds to the extracellular domain of ErbB3 receptor (page 462, col. 2).

The authors showed only weak agonistic affect on anchorage-dependent growth of cell lines expressing c-erbB3 protein and were "unable to show a significant effect of the SGP1 antibody on the kinase activity of the c-erbB3 receptor" (page 464, col. 1). They do not disclose a nucleic acid encoding the SGP1 antibody. They neither suggest nor disclose (1) the effects of an anti-ErbB3 antibody on heregulin binding or binding affinity, (2) an anti-ErbB3 antibody that reduces formation of an ErbB2-ErbB complex, or (3) an anti-ErbB3 antibody that reduces heregulin-induced ErbB2 activation in a cell expressing ErbB2 and ErbB3. In fact, Rajkumar et al. do not contemplate or suggest any association between ErbB2 and ErbB3, much less any heregulin-induced complex formation or ErbB2 activation. Thus, Rajkumar et al. do not suggest nor provide motivation for, much less disclose, Applicants' claimed invention.

Additional references are cited which disclose methods of obtaining gene sequences, antibodies, antibody fragments, and humanizing an antibody. None of the additionally cited disclosures, either alone or in any combination, cure the deficiencies of the Rajkumar et al. reference.

Orlandi et al. as a whole. Orlandi et al. (PNAS USA (1989) 86:3833-3837) generally disclose a method for obtaining heavy and light variable chain genes by PCR from a hybridoma cell. The authors do not contemplate, suggest, provide motivation for, nor disclose a nucleic acid encoding an antibody that binds ErbB3 and reduces heregulin-induced formation of an ErbB2-ErbB3 complex, or reduces heregulin-induced ErbB2 activation, or increases the affinity of heregulin or reduces binding of heregulin to ErbB3. The Orlandi et al. reference does not suggest or disclose Applicants' claimed invention nor does it cure the deficiencies of the Rajkumar reference or any of the other cited references.

Robinson et al. as a whole. Robinson et al. (US 5,618,920) disclose a method of secreting antibody heavy and light chain immunoglobulins from a prokaryotic host to produce an antibody. The patent disclosure does not contemplate, suggest, provide motivation for, nor disclose a nucleic acid encoding an antibody that binds ErbB3 and reduces heregulin-induced

formation of an ErbB2-ErbB3 complex, or reduces heregulin-induced ErbB2 activation, or increases the affinity of heregulin or reduces binding of heregulin to ErbB3. The Robinson patent does not suggest or disclose Applicants' claimed invention nor does it cure the deficiencies of the Rajkumar reference or any of the other cited references.

Ward et al. as a whole. Ward et al. (Nature (1989) 341:544-546) disclose a method of preparing VH domains using PCR, expressing the clones and secreting them from a prokaryotic host. The Ward disclosure does not contemplate, suggest, provide motivation for, nor disclose a nucleic acid encoding an antibody that binds ErbB3 and reduces heregulin-induced formation of an ErbB2-ErbB3 complex, or reduces heregulin-induced ErbB2 activation, or increases the affinity of heregulin or reduces binding of heregulin to ErbB3. The Ward et al. reference does not suggest or disclose Applicants' claimed invention nor does it cure the deficiencies of the Rajkumar reference or any of the other cited references.

Cabilly et al. as a whole. Cabilly et al. (US 4,816,567) disclose a method of preparing a chimeric antibodies by combining constant and variable antibody regions recombinantly. The Cabilly et al. disclosure does not contemplate, suggest, provide motivation for, nor disclose a nucleic acid encoding an antibody that binds ErbB3 and reduces heregulin-induced formation of an ErbB2-ErbB3 complex, or reduces heregulin-induced ErbB2 activation, or increases the affinity of heregulin or reduces binding of heregulin to ErbB3. The Cabilly patent does not suggest or disclose Applicants' claimed invention nor does it cure the deficiencies of the Rajkumar reference or any of the other cited references.

Queen et al. as a whole. Queen et al. (PNAS (1989) 86:10029-33) disclose a method of preparing a humanized antibody by combining the complementary-determining regions (CDRs) of the anti-Tac antibody with human framework and constant regions. The Queen et al. disclosure does not contemplate, suggest, provide motivation for, nor disclose a nucleic acid encoding an antibody that binds ErbB3 and reduces heregulin-induced formation of an ErbB2-ErbB3 complex, or reduces heregulin-induced ErbB2 activation, or increases the affinity of

heregulin or reduces binding of heregulin to ErbB3. The Queen reference does not suggest or disclose Applicants' claimed invention nor does it cure the deficiencies of the Rajkumar reference or any of the other cited references.

Boss et al. as a whole. Boss et al. (US 4,816,397) disclose a method of producing heterologous multichain proteins (such as immunoglobulins) in cells transformed with nucleic acids encoding the protein chains. The Boss et al. patent does not contemplate, suggest, provide motivation for, nor disclose a nucleic acid encoding an antibody that binds ErbB3 and reduces heregulin-induced formation of an ErbB2-ErbB3 complex, or reduces heregulin-induced ErbB2 activation, or increases the affinity of heregulin or reduces binding of heregulin to ErbB3. The Boss patent does not suggest or disclose Applicants' claimed invention nor does it cure the deficiencies of the Rajkumar reference or any of the other cited references.

Huston et al. as a whole. Huston et al. (US 5,258,498) disclose synthetic proteins having binding affinity for a pre-selected antigen and methods of designing the binding site of such proteins based on sequence analysis of the Fv region of preexisting antibodies or the DNA encoding them (col. 10, lines 9-11). The Huston et al. patent does not contemplate, suggest, provide motivation for, nor disclose a nucleic acid encoding an antibody that binds ErbB3 and reduces heregulin-induced formation of an ErbB2-ErbB3 complex, or reduces heregulin-induced ErbB2 activation, or increases the affinity of heregulin or reduces binding of heregulin to ErbB3. The Huston patent does not suggest or disclose Applicants' claimed invention nor does it cure the deficiencies of the Rajkumar reference or any of the other cited references.

Claims 22-33 and 36-51 are rejected over primary reference Rajkumar et al. in view of secondary references Orlandi, Robinson, Ward, Cabilly, Boss, Queen and Huston. The primary reference, Rajkumar et al., lacks any teaching of Applicants' claimed invention and is not itself sufficient to render Applicants' invention obvious. Contrary to the Examiner's assertion, however, none of the cited secondary references in any number or combination cures the deficiencies of the Rajkumar et al. reference. Rajkumar et al. do not suggest or disclose an

antibody that affects the binding of heregulin with ErbB3 nor do they disclose a nucleic acid that encodes such an antibody. Further, Rajkumar et al. do not contemplate an ErbB2-ErbB3 complex nor do they contemplate heregulin-induced formation or activation of an ErbB2-ErbB3 complex. As a result, these authors could not have contemplated, much less suggest, disclose or provide motivation to make, a nucleic acid encoding an ErbB3-binding antibody that reduces heregulin-induced formation of an ErbB2-ErbB3 protein complex or reduces heregulin-induced ErbB2 activation in a cell expressing ErbB2 and ErbB3.

None of the cited secondary references cure the deficiencies of the Rajkumar et al. reference. None of the cited secondary references contemplate or suggest, much less disclose, Applicants' claimed nucleic acid encoding an ErbB3 antibody that affects heregulin binding or affects heregulin-induced ErbB2-ErbB3 complex formation or ErbB2 activation. The teachings in the secondary references regarding methods for obtaining heavy and light chain gene sequences (Orlandi), antibody production from a prokaryotic host (Robinson), VH domain production (Ward), chimeric antibody production (Cabilly), humanized antibody production (Queen), heterologous multichain protein production (Boss), or methods of obtaining the sequence of Fv regions from hybridoma mRNA (Huston) apply to antibodies in general and offer nothing with respect to heregulin binding or heregulin-induced ErbB2-ErbB3 complex formation or ErbB2 activation. When the secondary references are combined with the disclosure of the Rajkumar reference, the combination cannot and does not yield Applicants' claimed invention nor render it obvious because none of the references alone or in any combination contemplate affects on heregulin binding nor affects on heregulin-induced ErbB2-ErbB3 complex formation or ErbB2 activation and, thus, cannot cure the deficiencies of the Rajkumar et al. citation. As a result, the Examiner has failed to support a prima facie obviousness rejection of claims 22-33 and 36-51 and the rejection should be withdrawn, which action is respectfully requested. Applicants respectfully request allowance of the claims.

One of ordinary skill in the art would not have been motivated to nor have a reasonable expectation of success for obtaining a nucleic acid encoding an antibody that affects heregulin-

induced formation of an ErbB2-ErbB3 complex or ErbB2 activation because an ErbB2-ErbB3 complex was not contemplated or suggested, much less disclosed by Rajkumar et al. nor by any of the secondary references. None of the references disclose an association of ErbB3 with ErbB2 and, as a result, could not have provided the ordinarily skilled artisan with any motivation or reasonable expectation of success for obtaining a nucleic acid encoding an antibody that affects heregulin-induced ErbB2-ErbB3 complex formation or ErbB2 activation as Applicants have claimed. With respect, the Examiner improperly uses hindsight to support the rejection. As a result, no motivation is provided by the cited references, hindsight is improperly used to make the rejection, and the rejection should be withdrawn, which action is respectfully requested. Applicants respectfully request allowance of the claims.

Claims 34 and 35 are free of the prior art, but objected to for being dependent from a rejected base claim (claim 22). Applicants believe that claim 22 is allowable based on the above arguments, thereby rendering claims 34 and 35 allowable as well. Withdrawal of the objection and allowance of the claims is respectfully requested.

SUMMARY

Claims 22-51 are pending in the application. No claim is amended. The rejection of claims 22-33 and 36-51 under Section 103(a) and the objection to claims 34 and 35 have been overcome by the discussion above. Withdrawal of the rejection and objection and allowance of the claims is respectfully requested.

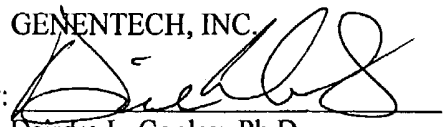
If in the opinion of the Examiner, a **telephone conference** would expedite the prosecution of the subject application, the Examiner is **strongly encouraged** to call the undersigned at the number indicated below.

This response/amendment is submitted with a transmittal letter and petition for three-month extension of time and fees. In the unlikely event that this document is separated from the transmittal letter or if fees are required, applicants petition the Commissioner to authorize charging our Deposit Account 07-0630 for any fees required or credits due and any extensions of time necessary to maintain the pendency of this application.

Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,
GENENTECH, INC.

Date: May 4, 2004

By: 
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